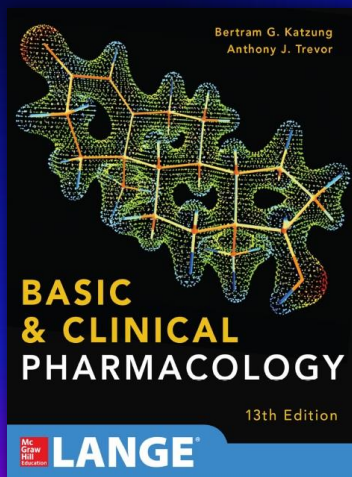


General Anesthetic Drugs

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Reference



- Basic and Clinical Pharmacology
- B.G. Katzung, MD, PhD
- Chapter 25

What is general anesthesia?

- Absence of sensation and consciousness
- Consciousness has different levels
- General anesthesia characterized by five primary effects
 - Unconsciousness
 - Amnesia
 - Analgesia
 - Inhibition of autonomic reflexes
 - Skeletal muscle relaxation



Anesthesia stages

- Stage 1 - narcosis, sedation, analgesia, hallucination, amnesia
- Stage 2 - uninhibited response, delirium, excitement
- Stage 3 - surgical stage
 - Plane 1 - loss of pain response
 - Plane 2 - surgical plane
 - Plane 3 - beginning of respiratory paralysis/pupil dilation
 - Plane 4 - cyanosis, non-responsive pupils
- Stage 4 - paralysis of brain respiratory centers

Historical Perspective

Original discoverer of general anesthetics

- Ether
 - Crawford Long: 1842, anesthesia
- Chloroform
 - James Simpson: 1847
- Nitrous oxide
 - Horace Wells



Types of anesthetic agents

- There are two major types of anesthetics used for general anesthesia

1. Inhalation anesthetics

2. Intravenous anesthetics

1- Inhalational Anesthetic Drugs

Volatile agents:

- Isoflurane
- Sevoflurane
- Desflurane
- Enflurane
- Halothane (Fluthane)

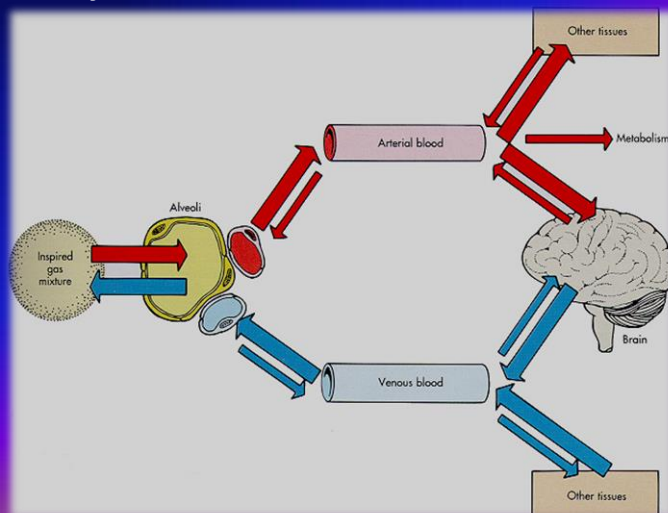
Halogenated **liquid** hydrocabons

Gases:

- Nitrous Oxide (N_2O)
- Xenon
In the near future ???

Inhalational Anesthetic Drugs

Pathway for General Anesthetics



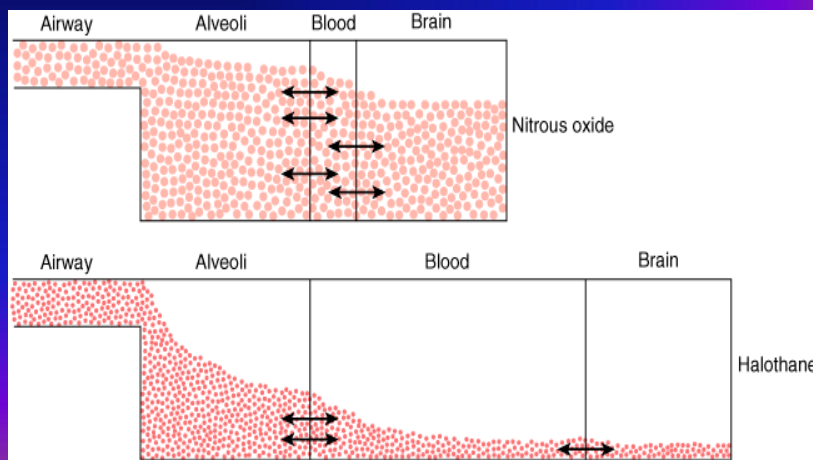
Pharmacokinetics

Factors that Influence Absorption

- **Solubility** of Drug in Blood
 - **Low Solubility** in Blood: → Rapidly Saturate blood
 - Rapid rise of arterial partial pressure
 - **Fast Onset of Action**
- Blood / gas partition coefficient
 - **Index of Solubility**
 - Defines relative affinity of an anesthetic for blood compared with that of inspired gas

Pharmacokinetics

The more soluble: The more time to saturate blood

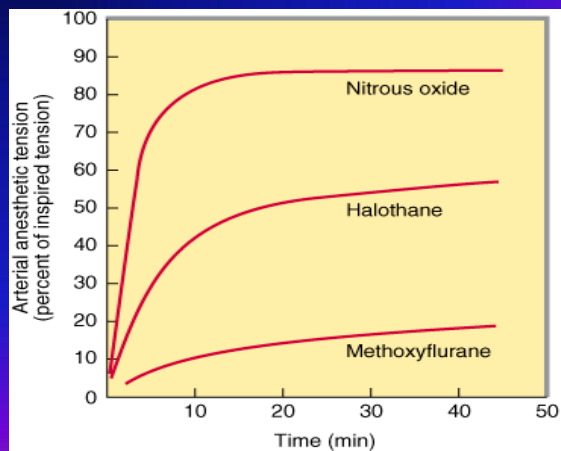


Pharmacokinetics

- **Low:** rapid onset of anesthesia & recovery
 - Desflurane, sevoflurane, nitrous oxide
- **Moderate:** intermediate onset of anesthesia
 - Enflurane, halothane, isoflurane
- **High:** slow onset of anesthesia
 - Methoxyflurane, ether

There is inverse relationship

Pharmacokinetics



Pharmacokinetics

Absorption

- Drug concentration in inspired air:
 - ↑ **Drug doses**: ↑ Rate of transfer into blood
 - ↑ **Rate of anesthesia induction**
- Pulmonary ventilation
- **Hyperventilation**: ↑ **Rate of anesthesia induction**
 - Prominent for drugs that normally have a slow onset
 - Opioid analgesics: → hypoventilation
 - ↓ Rate of anesthesia induction & recovery

Pharmacokinetics

Absorption

- ↑ Pulmonary blood flow (↑cardiac output)
 - ↑ Time for blood saturation
 - ↓ Rate of rise in anesthetic tension
 - ↓ Rate of anesthesia induction
 - Significant for drugs with moderate-to-high solubility
- Circulatory shock
 - ↓ Cardiac output & hyperventilation
 - ↑ Induction of anesthesia with halothane & isoflurane

Pharmacokinetics

Rate of entry into the brain

- Solubility of gas in blood (blood/gas coefficient)
 - Less soluble; faster
- Concentration in the inspired air
 - Increased rate; faster
- Pulmonary ventilation
 - Increased rate; faster
- Pulmonary blood flow
 - Decreased rate; faster
- Cardiac output
 - Decreased output; faster

Pharmacokinetics

Elimination

- **Lungs** is the major route of elimination
- Hepatic metabolism may also contribute to elimination of some volatile anesthetics
 - ↑ Rate of elimination: ↑ **Rate of recovery**
- Factors controlling rate of recovery
 - ↓ Blood solubility : ↑ Rate of recovery
 - ↑ Duration of exposure to drug: ↓ Rate of recovery

Pharmacokinetics

Hepatic metabolism

- Enflurane & Sevoflurane
 - Low level fluoride ions: not toxic
- Sevoflurane
 - Degraded by contact with CO₂
 - Yielding a vinyl ether called “Compound A”
 - Cause Renal Damage if high concentrations are absorbed

Measures of Anesthetic Potency

MAC: Minimal Alveolar Concentration

- The concentration of anesthetic at 1 atm at which 50% of the patients do not move on skin incision
- Equivalent to ED50
- MAC decreases in some conditions
 - Elderly patients
 - Hypothermia
 - Co-administration with opioid analgesics
 - Co-administration with sympatholytics
 - Co-administration with sedative-hypnotics

Mechanism of action

- Facilitate action of GABA
- High doses: Directly activate GABA receptors
- Hyperpolarization via K channel activation
- ↓ Duration of nicotinic receptor opening
- ↑ Glycine receptor activating



Organ system effects

Cardiovascular system

- ↓ BP; most of them
- Bradycardia; halothane (direct vagal stimulation)
- ↑ HR & BP; desflurane & isoflurane
 - Transient sympathetic activation with elevations in catecholamine levels
- Ventricular arrhythmias; halothane & isoflurane

Organ system effects

Respiratory System

- Respiratory depression
 - Isoflurane & Enflurane
- All increase resting level of Pa CO₂
- ↓ Mucociliary function in airway
- Bronchodilation
 - Halothane & Sevoflurane
- Some are Pungent
 - Desflurane

Organ system effects

Brain

- ↑ Cerebral blood flow → ↑ ICP
 - Least likely; nitrous oxide
 - Less with desflurane & sevoflurane
- Seizure-like EEG activity
 - Not seen with desflurane
- Analgesic & amnesic effect
 - Specific to nitrous oxide

Organ system effects

Kidney

- ↓ GFR & renal blood flow

Liver

- ↓ Hepatic blood flow

Uterine smooth muscle

- Relaxation
- Nitrous oxide: little effect

Side effects

- **Hepatotoxicity**
 - Halothane
 - More likely in obese with previous exposure during short time interval
- **Nephrotoxicity:** methoxyflurane
- **Malignant hyperthermia:** rare
- **Megaloblastic anemia:** nitric oxide
 - ↓ Methionine synthase activity

2-Intravenous agents

- Ultra short barbiturate
- Benzodiazepines
- Opioid analgesics
- Propofol
- Ketamine
- Etomidate

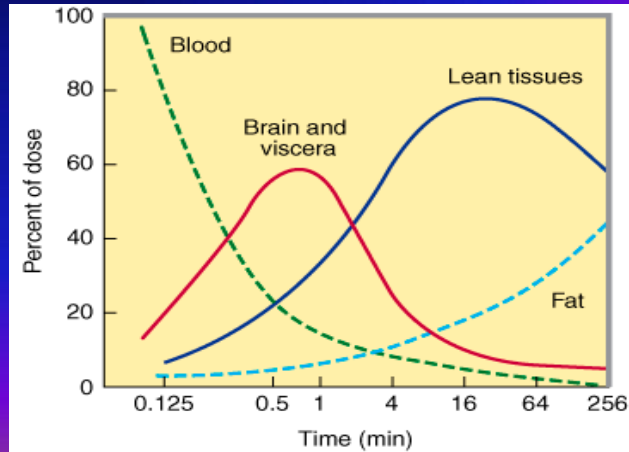
Ultra short barbiturate

- **Thiopental**: commonly used for induction of anesthesia.
- **Methohexital**
- Has high lipid solubility and rapidly crosses BBB
- Produces unconsciousness in < 1 minute
- Thiopental is rapid- (20 sec) & short-acting
- Mechanism of action ???



Ultra short barbiturate

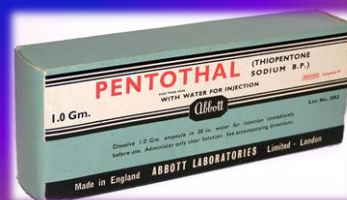
- Redistribution of thiopental



Ultra short barbiturate

Side effects

- Myocardium depression
- ↓ BP & cardiac output
- Respiratory depressant effect
- ↓ Cerebral blood flow
 - It does not increase ICP
- ↓ Hepatic blood flow
- ↓ GFR



Benzodiazepines

- **Peanesthetic** medications
- Due to their sedative, anxiolytic, and amnestic effects
 - Diazepam
 - Lorazepam
 - Midazolam
- **Midazolam** is the choice for parenteral anesthesia
- Has a more rapid onset
- Shorter elimination half-life (2–4 hours)
- Mechanism of action ???
- Side effects ???

Benzodiazepines

Midazolam

- A water-soluble benzodiazepine
- Dose related effects:
 - Anti anxiety → Sedation → Amnesia → Deep sedation
- Conscious sedation
- Side effect:
 - Respiratory arrest, respiratory depression
 - Hypotension in neonates
- Antidote???



Opioid analgesics

- Morphine
- Fentanyl
- Alfentanil
- Sufentanil
- Remifentanyl
 - Potent and extremely short-acting opioid
 - Minimum residual ventilatory depression

Propofol

- Commonly used IV anesthetic
- Rapid onset of action (similar to IV barbiturates)
- More rapid recovery than barbiturates
- Effective in producing prolonged sedation
- A CNS depressant
- GABA-A receptor activator (unknown)
- Not analgesic effect
- Anti-emetic → ↓ postoperative N & V
- Allergy to its solvent

Propofol

Side effects

- Pain at the site of injection is the most common adverse effect of bolus administration
- Effects on respiratory function are similar to those of thiopental
- ↓ BP & venodilation
- Greater direct negative inotropic effects than other IV anesthetics
 - Hypotension, arrhythmia
- Rash, hyper-salivation, apnea, confusion

Ketamine

- The only IV anesthetic that possesses
 - Both anesthetic & analgesic effect
 - Ability to produce dose-related cardiovascular stimulation:
 - HR, BP, and cardiac output
 - Dangerous for hypertensive and IHD
 - It blocks NMDA receptor of glutamic acid

Ketamine

- Myocardial stimulation, Hypertension
- ↑ ICP, Cerebral Blood flow, oxygen consumption
- ↓ Respiratory Rate
- Postoperative Disorientation
- Sensory and Perceptual Illusions
- Vivid Dreams
- Delirium



Etomidate

- GABA-A receptor modulator
- Fast onset of action
- Not analgesic effect
- Low myocardium depression

Side effect

- Nausea
- Pain in injection site
- Adrenal suppression



Anesthesia regimens

- Balanced anesthesia:
 - Benzodiazepine
 - Short acting barbiturate
 - N₂O
 - Opiate
 - Muscle relaxant
- Conscious sedation:
 - Benzodiazepine
 - Local anesthetic